REMARKS

Claims 1-8 are pending. Claims 9-31 have been previously withdrawn. Claim 32 has been previously cancelled. Claims 1, 4, 5, 6 and 7 have been amended. Support for the amendments are provided in the specification. For 2-mercaptoethanesulfonic acid, see for example, page 21, line 8 of the Application. The term "non-covalent binding" is inherent in the description on page 18. For "under conditions in which the carrier-ligand remains non-covalently bound to the matrix" see, for example, page 23 of the Application.

Rejection under 35 U.S.C. §112

Claims 4, 5 and 7 have been amended to introduce antecedent basis for "matrix-binding molecule".

Claims 1-8 have been rejected as indefinite on the basis of the meaning as defined in the specification page 20, lines 5-8. The definition refers to inteins in InBase, a database maintained by applicants for public use. The specification on page 30 of the application further describes how a carrier-ligand can be made in a manner that utilizes a C-terminal thioester on the carrier where the C-terminal thioester is the product of intein cleavage in the presence of a thiol reagent of a carrier intein fusion protein. Reference is made to IMPACT (page 30), which is a kit that was on sale by New England Biolabs (NEB) prior to filing the present application and is described in the NEB catalog (for example, see page 176 of the 2005/2006 NEB catalog).

Formation of a protein from a protein-intein fusion in the presence of a thiol reagent is described in detail in the specification and is also a well-known procedure in the prior art that was pioneered by applicants. Nock et al. describes the same procedure using applicants' technology and refers to references and patents by applicants in paragraphs 0055- 0059. Muir describes the use of IMPACT (column 13, line 26 of the reference) sold by NEB to ligate a protein with a C-terminal thioester to a synthetic 34mer with a nucleophilic group (column 15, line 29 of the reference).

In light of the description in the application of page 30, it should be clearly understood to a person of ordinary skill in the art what constitutes a carrier-intein or ligand-intein fusion protein suitable for generating a C-terminal thioester on the carrier or ligand after cleavage of the intein in the presence of a thiol reagent.

Rejection under 35 U.S.C. §102(e)

The Examiner has rejected claims 1-8 as anticipated by Muir et al. and Nock et al.

Muir et al.

Applicants respectfully submit that Muir et al. does not disclose the claimed invention for reasons that include the following:

In Figure 2A, steps (3) and (4), Muir et al. prepares a peptide that is a synthetic peptide having two ends. One end is covalently linked to the matrix (see for example, column 20, line 1). The other end has a nucleophilic group for binding the thiolester on a

recombinant protein be it an antigen or an antibody. Moreover, Muir et al. states a strong preference for thiophenol for cleavage and ligation.

> Surprisingly, thiophenol was found to be the only co-factor tested that supported both efficient cleavage and efficient ligation. (Muir et al. column 14, line 49)

Muir et al. does not recite 2-mercaptoethanesulfonic acid (MESNA) in the list of possible alternative thiol reagents (column 8, line 48). However, applicants have previously found that MESNA is significantly more effective than thiophenol or DTT (used by Muir et al. in the examples).

In contrast to Muir et al., the carrier of the present claimed invention is bound non-covalently to a matrix.

In contrast to Muir et al., the carrier of the present claimed method has a thiol group, which enables it to bind to a ligand having a nucleophilic group. In Muir et al., it is the ligand that has a thiol group.

In contrast to Muir et al., the ligand and not the carrier in the present claimed method can be recombinant or chemically synthesized as long as it contains the nucleophile group. In Muir et al., the carrier is chemically synthesized.

The present claimed invention is an improvement over the method described by Muir et al. for reasons that include the following. The presence of the thiol group on the carrier and the nucleophilic group on the ligand enhances the flexibility of the substrate as an

affinity substrate. For example, the ligand is not limited to a protein or peptide that must be made recombinantly to generate the C-terminal thiol. Instead, the ligand could be an antigen that is a chemical entity and is not necessarily a product of genetic engineering. Moreover, according to the present claimed invention, the carrier is capable of binding to a matrix non-covalently and remaining attached to the column under conditions where the ligand-binding molecule is eluted (page 23 of the Application).

Nock et al.

This reference describes how arrays of polypeptides can be arranged on a support surface. Figure 1 of the reference does not utilize a thioester intermediate. Figures 2 and 3 of the reference describe cleavage of a peptide-intein fusion to generate a peptide having a thioester. In Figure 2, the polypeptide binds to A before binding to a substrate. In Figure 3, A is already anchored to a substrate before the polypeptide binds.

In contrast to the claimed method, Nock et al. describe an array that is essentially the same as the array described by Muir et al. In both references, the array is formed by reacting a protein (ligand) that has a thioester to an anchor molecule with a nucleophilic group. A disadvantage of this arrangement is that the nature of the ligand is constrained in that it must be made recombinantly as a fusion protein, which is then cleaved. Another constraint is that if the anchor is a small molecule as described by both Muir et al. and Nock et al., it must be attached to the matrix by a covalent linkage as small molecules generally do not readily bind non-covalently with affinity to standard substrates that might be used in an array.

As discussed above, the present claimed method relies on the carrier having a thioester reactive group. It is the carrier that must be made recombinantly. In contrast, the ligand, which in the claimed method carries the nucleophile, can be made recombinantly or by chemical synthesis. It can be modified as desired for studying protein-protein interactions between ligand and ligand-binding domains or for use in drug screening where modifications such as phosphorylation, methylation and acetylation may have considerable biological impact.

For the reasons discussed above, the present claimed method is a patentably distinct improvement over the cited references.

CONCLUSION

For the reasons set forth above, Applicants respectfully request that the rejections set forth in the Office Action of August 28, 2006 be withdrawn and submit that this case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this Application is earnestly solicited.

Applicants petition for an extension of three months and enclose a check for $510 covering the extension fees. Applicants authorize that any additional fees that may be due be charged to deposit account number 14-0740.

Respectfully submitted,

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